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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,173	01/14/2002	Michela Seveso	9701-11	5272

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/743,173	SEVESO ET AL.	
	Examiner	Art Unit	
	J. E. ANGELL	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,44-52 and 55-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,44-52 and 55-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 3/24/2010.

The amendment filed 3/24/2010 is acknowledged. The amendment has been entered.

Claims 1, 44-52, 55-65 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. Claims 1, 44-51, 55, 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO99/01579 (Teng et al., of record) for the reasons of record.

2. Claims 1 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO99/01579 (Teng et al.) in view of GB2319773A (Lewin et al., of record) for the reasons of record.

3. Claims 57, 58, 63, 64, 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO99/01579 (Teng et al.) in view of Akhtar (J. Drug Targeting 1998, of record)

As previously indicated, WO99/01579 (Teng et al.) teaches a composition and method for enhancing the transport of a nucleic acid drug, especially antisense oligonucleotides, in an animal (e.g., see abstract). Teng et al. teaches that the composition that is administered to the animal comprises "various fatty acids… and other penetration enhancers" (e.g., see abstract); and specifically indicates that the fatty acid/penetration enhancer can be caprylic acid, including a sodium salt thereof (e.g., see page 10, lines 17-31; page 29, line 30 through page 30, line 25). Teng et al teach that the method can be used for delivery to the alimentary canal, including "any and all of its portions or segments, e.g.… the small and large intestines." (See page 7 lines 5-11). Teng et al. specifically teaches, "More specifically, the present invention is directed to the use of various fatty acids… and other penetration enhancers… to enhance the stability of oligonucleotides and other nucleic acids and/or their transport across and/or into cells of the alimentary canal." (Emphasis added, see page 1, lines 12-18). It is noted that oral administration of the composition would necessarily result in contacting epithelial cells of the small intestines with the composition which would be effective for facilitating the intracellular delivery of the nucleic acid. Teng et al also teach that the antisense oligonucleotide can comprise a modified backbone chemistry, such as a phosphorothioate modified backbone (e.g., see page 18). (Also see p. 17, lines 12-27; p. 29, line 30 through p. 30, line 30; claims 1-25, especially claims 1, 2, 4, 5, 14, 16, 25).

Teng et al also teaches that the enhancer can be caproate (C10), which is encompassed by claim 1, wherein the concentration of caproate is 1% of the solution (i.e., about 58mM). Furthermore, Teng et al teach that the composition was made by 500mg sodium caprate with 250ul of a solution containing 200mg/ml (i.e., 50mg) of an antisense oligonucleotide (see page

47 lines 4-9). Therefore, Teng et al teach that the molar ration of the enhancer (caprate) and the nucleic acid based drug (ISIS 2302) is within the range set forth in claim 55 (1:100 to 100:1).

Teng et al does not teach that: (1) the oligonucleotide is complexed with a cationic lipid or a polymer system; (2) an endosomal escape/nuclear accumulation agent can be used to facilitate delivery; (3) a condensing agent can be used to condense the oligonucleotide and facilitate delivery; and (4) a condensing agent can be used to condense the oligonucleotide and the oligonucleotide is complexed with a cationic lipid to facilitate delivery.

However, Akhtar teaches a number of different means for facilitating delivery of antisense oligonucleotides into cells including the use of cationic lipids, polymer microspheres, as well as the use of agents to improve endosomal exit. Akhtar also teaches that polylysine, which one of skill in the art would recognize as a condensing agent, can improve cellular uptake of antisense oligonucleotides. (See page 228-230, section titled “Cellular Delivery of ODNs”, including Table 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at he time of filing that any of the means of facilitating delivery of antisense oligonucleotides, taught by Akhtar (and combinations thereof) could be used to facilitate the delivery of the oligonucleotide compositions taught by Teng et al., with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to use those means for facilitating delivery of antisense oligonucleotides because Akhtar teaches that they improve cellular delivery of antisense oligonucleotides.

Furthermore, although Teng teaches that the C10 enhancer can be used at a concentration of about 58mM, Teng does not teach to use "about 0.013mM to 13mM" of C10 enhancer, as is indicated in claim 1.

However, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to perform routine experimentation to determine the optimum and/or workable ranges of concentration for the C10 enhancer with a reasonable expectation of success.

As noted in In re Aller, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Accordingly, routine optimization is not considered inventive and no evidence has been presented that the selection the specific concentration range was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As such the instant claims are obvious in view of the teaching of Teng.

Claims 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO99/01579 (Teng et al.) in view of Akhtar (J. Drug Targeting 1998, of record) and Akhtar et al. (Int. J. Pharmaceutics, 1997; or record).

WO99/01579 (TENG et al.) teaches a composition and method for enhancing the transport of a nucleic acid drug, especially antisense oligonucleotides, in an animal (e.g., see abstract). Teng et al. teaches that the composition that is administered to the animal comprises "various fatty acids… and other penetration enhancers" (e.g., see abstract); and specifically

indicates that the fatty acid/penetration enhancer can be caprylic acid, including a sodium salt thereof (e.g., see page 10, lines 17-31; page 29, line 30 through page 30, line 25). Teng et al teach that the method can be used for delivery to the alimentary canal, including "any and all of its portions or segments, e.g.… the small and large intestines." (See page 7 lines 5-11). Teng et al. specifically teaches, "More specifically, the present invention is directed to the use of various fatty acids… and other penetration enhancers… to enhance the stability of oligonucleotides and other nucleic acids and/or their transport across and/or into cells of the alimentary canal." (Emphasis added, see page 1, lines 12-18). It is noted that oral administration of the composition would necessarily result in contacting epithelial cells of the small intestines with the composition which would be effective for facilitating the intracellular delivery of the nucleic acid. Teng et al also teach that the antisense oligonucleotide can comprise a modified backbone chemistry, such as a phosphorothioate modified backbone (e.g., see page 18). (Also see p. 17, lines 12-27; p. 29, line 30 through p. 30, line 30; claims 1-25, especially claims 1, 2, 4, 5, 14, 16, 25).

Teng et al does not teach that: (1) the oligonucleotide is complexed with a cationic lipid or a polymer system; (2) an endosomal escape/nuclear accumulation agent can be used to facilitate delivery; (3) a condensing agent can be used to condense the oligonucleotide and facilitate delivery; and (4) a condensing agent can be used to condense the oligonucleotide and the oligonucleotide is complexed with a cationic lipid to facilitate delivery.

However, Akhtar teaches a number of different means for facilitating delivery of antisense oligonucleotides into cells including the use polymer microspheres. (See page 228-230, section titled "Cellular Delivery of ODNs", including Table 1).

Furthermore, Akhtar et al. (J Int Pharm, 1997) specifically teaches that biodegradable polymers, specifically PLGA, can be used to facilitate delivery of antisense oligonucleotides into cells, wherein the antisense oligonucleotide is complexed with (i.e., entrapped in) the polymer (e.g., see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that antisense oligonucleotide composition (such as those taught by Teng) could be complexed with (entrapped in) a biodegradable polymer, such as PLGA (as taught by Akhtar et al.) to facilitate the delivery of the oligonucleotide compositions, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to use the PLGA polymer of Akhtar et al. for facilitating delivery of the antisense oligonucleotide composition of Teng because Akhtar et al. teaches that PLGA improves cellular delivery of antisense oligonucleotides.

Additionally, furthermore, although Teng teaches that the C10 enhancer can be used at a concentration of about 58mM, Teng does not teach to use "about 0.013mM to 13mM" of C10 enhancer, as is indicated in claim 1.

However, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to perform routine experimentation to determine the optimum and/or workable ranges of concentration for the C10 enhancer with a reasonable expectation of success.

As noted in In re Aller, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Accordingly, routine optimization is not considered inventive and no evidence has been presented that the selection the specific concentration range was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As such the instant claims are obvious in view of the teaching of Teng.

Claims 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO99/01579 (Teng et al., see above) in view of Nakashima et al. (J. Pharm. Sci., 1995).

WO99/01579 (TENG et al.) teaches a composition and method for enhancing the transport of a nucleic acid drug, especially antisense oligonucleotides, in an animal (e.g., see abstract). Teng et al. teaches that the composition that is administered to the animal comprises "various fatty acids… and other penetration enhancers" (e.g., see abstract); and specifically indicates that the fatty acid/penetration enhancer can be caprylic acid, including a sodium salt thereof (e.g., see page 10, lines 17-31; page 29, line 30 through page 30, line 25). Teng et al teach that the method can be used for delivery to the alimentary canal, including "any and all of its portions or segments, e.g.… the small and large intestines." (See page 7 lines 5-11). Teng et al. specifically teaches, "More specifically, the present invention is directed to the use of various fatty acids… and other penetration enhancers… to enhance the stability of oligonucleotides and other nucleic acids and/or their transport across and/or into cells of the alimentary canal." (Emphasis added, see page 1, lines 12-18). It is noted that oral administration of the composition would necessarily result in contacting epithelial cells of the small intestines with the composition which would be effective for facilitating the intracellular delivery of the nucleic acid. Teng et al

also teach that the antisense oligonucleotide can comprise a modified backbone chemistry, such as a phosphorothioate modified backbone (e.g., see page 18). (Also see p. 17, lines 12-27; p. 29, line 30 through p. 30, line 30; claims 1-25, especially claims 1, 2, 4, 5, 14, 16, 25).

Teng et al does not teach that a P-glycoprotein inhibitor is administered with the antisense oligonucleotide composition.

However, Nakashima et al. teach that verapamil, a P-glycoprotein inhibitor, can be used in low doses in combination with antisense oligonucleotides to increase the efficacy of the antisense oligonucleotide treatment (e.g., see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to use verapamil, a P-glycoprotein inhibitor, in combination with antisense oligonucleotide composition taught by Teng, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to use the P-glycoprotein inhibitor in combination with antisense oligonucleotide composition because Nakashima teaches that low doses of the inhibitor increases the efficacy of the antisense oligonucleotide.

Furthermore, although Teng teaches that the C10 enhancer can be used at a concentration of about 58mM, Teng does not teach to use "about 0.013mM to 13mM" of C10 enhancer, as is indicated in claim 1.

However, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to perform routine experimentation to determine the optimum and/or workable ranges of concentration for the C10 enhancer with a reasonable expectation of success.

As noted in In re Aller, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Accordingly, routine optimization is not considered inventive and no evidence has been presented that the selection the specific concentration range was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As such the instant claims are obvious in view of the teaching of Teng.

Response to Arguments

4. Applicant's arguments filed 3/24/2010 have been fully considered but they are not persuasive.

Applicants note that Teng does not provide any particular examples for a C8 enhancer and only provides guidance for using a C10 enhancer at higher concentrations than is claimed. Applicants argue that Teng teaches a way from using lower concentrations of enhancer below that disclosed in the Examples and that there is no motivation to use lower concentrations.

This is not persuasive because although the Examples for a C10 enhancer do use a higher concentration than is now claimed, this does not equate to a teaching away from using a lower concentration. A true teaching away would indicate doubt that lower concentration would work. In other words, a teaching away would lead one of ordinary skill in the art to believe that using concentrations within the claimed range would be ineffective and thus should not be used. This is not the case here where one of ordinary skill in the art would expect that the use of any amount of enhancer would still result in effective delivery. Furthermore, although Teng indicates that

higher concentrations result in more effective delivery, this does not mean that there would be no motivation to use lower concentrations of enhancer. One of ordinary skill in the art would have been motivated to determine not just the concentration that is most effective for enhancing delivery, but to also determine the minimal effective concentration because the use of lower concentrations would cost less and could potentially save money. Furthermore, knowing the full range of effective concentration could aid in determining which concentrations would be effective if higher concentrations resulted in adverse side effects.

Furthermore, regarding that lack of specific guidance on enhancers for C8, it is noted that the claimed concentration range for C8 is 0.12-120mM encompasses a higher concentration than what is claimed for C10s (.013-13mM) and the concentrations taught by Teng for the C10 enhancer would be within the range claimed for the C8 enhancer.

Applicants argue that the claimed concentration for C10 is about 4 to 4000 times lower than the lowest concentration used by Teng for C10. In response, it is noted that the claims encompass "about 0.0.13mM to 13mM" when the enhancer is a C10 enhancer and "0.12mM to 120mM" when the enhancer is a C8 enhancer. The lowest concentration used in the Examples of Teng for the C10 (caprate) is 0.5% (about 29mM) (e.g., see Formulations 3, 15, 17), Thus the lowest concentration of a C10 used in the formulations of Teng is less than 3 times the highest concentration of a C10 enhancer encompassed by the claims. Furthermore, looking at the results presented in Table 13 of Teng, it is clear that formulations 15 and 17 (which have 0.5% caprate (C10)) shows a higher absorption of oligonucleotide (30.6% and 23.0%, respectively) than formulation 16 (1.0% caprate; 19.7%). These results do not support a contention that Teng teaches away from using lower concentrations of a C10 enhancer.

Therefore, Applicants arguments are not persuasive.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. ANGELL whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 7:00 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. ANGELL/
Primary Examiner, Art Unit 1635